"Do I have a hard head?" asked Nathan Klein. "My wife always says I have a hard head."

"No, it's pretty average," said Dr. Michael G. Kaplitt. "This is one of the few situations in life where you want to be average."

Dr. Kaplitt had just bored a hole about the size of a quarter through the top of Mr. Klein's skull, in preparation for an ambitious experiment: the infusion deep into the brain of 3.5 billion viral particles, each bearing a copy of a human gene meant to help relieve the tremors, shuffling gait and other abnormal movements caused by Parkinson's disease.

Yesterday at New York-Presbyterian Hospital, Mr. Klein, 55, an independent television producer from Port Washington, N.Y., became the first person to undergo gene therapy for Parkinson's. Despite the checkered history of gene therapy experiments, the Food and Drug Administration approved this procedure for 12 people with severe Parkinson's.

The experiment is a Phase 1 trial, meaning that its main goal is to determine safety, not efficacy. But of course the researchers and their subjects will also be looking for signs that the treatment works. That should become clear within three months, said Dr. Kaplitt, who is an assistant professor at Weill Cornell Medical Center and director of stereotactic and functional neurosurgery at New York-Presbyterian Hospital. "My goal is not to try to cure Parkinson's disease," Dr. Kaplitt said. "It's to provide a better treatment that we can build on to make the next advance."

But some leading experts in gene therapy and Parkinson's disease expressed concern.

They said the experiment was going forward without evidence in monkeys that it could work and that it held the possibility of harm: viruses spreading in the brain, or gene-treated cells churning out huge quantities of proteins that inhibit brain cells from firing.

"This is a crazy experiment," said Dr. C. Walter Olanow, who is a professor and the chairman of the department of neurology at Mount Sinai School of Medicine.

In an interview before the operation, Mr. Klein said he had been fully informed of potential risks.

"I do hope that it does something, whether it will be 10 percent better, 25 percent, 50 percent or more, I hope that this will work," he said. "But I'm the first and I'm their monkey."

About 1.5 million Americans have Parkinson's disease. Tremors are its hallmark, familiar to anyone who has seen the shaking limbs of people with the disorder, like the actor Michael J. Fox or former Attorney General Janet Reno. But other symptoms can be just as troubling, if not more so: people become stiff and can suddenly freeze, unable to move, and many find that they can walk only by shuffling along in tiny steps, which
sometimes accelerate beyond their control and send them sprawling. Some develop cognitive problems or dementia.

The disease occurs because nerve cells die in a part of the brain, the substantia nigra, leading to a shortage of dopamine, a chemical messenger that helps carry signals between various brain regions involved in movement.

Drugs can help to control the abnormal movements for a time. The best known, L-dopa, turns to dopamine in the body. But all drugs have side effects. Mr. Klein, for instance, who has had Parkinson's for 10 years and tried 8 or 10 drugs, has suffered from constipation, weight gain, insomnia, dry mouth and fatigue. Other patients develop new movement disorders from L-dopa. And over time, the drugs can lose their effectiveness.

Surgery to destroy bits of the brain that touch off tremors can help, but has its own risks. Fetal cell implants have not helped patients overall and have led to severe movement problems in some. Pacemaker-like devices known as deep brain stimulators have shown promise for some patients who have run out of drug options. But implants pose a risk of infection, and devices can fail.

Dr. Kaplitt and Dr. Michael During, a professor of molecular medicine at the University of Auckland, in New Zealand, with whom he has been collaborating for 10 years, saw plenty of room for improvement in treating Parkinson's.

They and their colleagues suspected that dopamine was not the best target for gene therapy, because patients would probably have been taking dopamine for years and might be resistant to it.

They decided that it made more sense to provide a gene that would enable cells in an overactive region of the brain, the subthalamic nucleus, to make a different messenger chemical, one that would calm the cells themselves and other overstimulated brain regions. The gene they chose is called GAD, for glutamic acid decarboxylase, an enzyme that helps produce a chemical messenger called GABA, for gamma aminobutyric acid.

Genes alone cannot get into cells, but viruses can, and in gene-therapy experiments viruses are commonly used to carry genes to their destination. Dr. Kaplitt and Dr. During chose the virus AAV, or adeno-associated virus. It does not cause disease in people, Dr. Kaplitt said, and its genetic material is removed.

In experiments in mice with a disorder that is intended to mimic Parkinson's, the gene therapy helped all the animals somewhat and helped about half of them a great deal, Dr. Kaplitt and Dr. During reported last October in the journal Science. They have also tested the treatment in monkeys but have declined to discuss the results, because they have not yet been published.

Dr. Kaplitt and Dr. During founded a company, Neurologix, to produce the gene therapy. The company, run by Dr. Kaplitt's father, is paying for the Phase 1 study. Dr. During is a paid consultant to the company. Dr. Kaplitt is not, though he was in the past. He and Dr. During do not recruit patients for gene therapy. Patients are referred by -- and followed by -- Dr. David Eidelberg and Dr. Andrew Feigin from North Shore-Long Island Jewish Hospital. Neither has any connection to Neurologix.

Many researchers have had qualms about gene therapy since 1999, when a teenage boy, Jesse Gelsinger, died in a gene therapy experiment at the University of Pennsylvania. More recently, several children in France who were successfully treated with gene therapy
therapy for an immune disorder later developed a leukemia-like disease.

In this case, some experts say a gene therapy experiment is particularly questionable because Parkinson's patients could have brain stimulators implanted instead.

"You don't have to take the risk of putting in a virus and you don't have to take the risk that it's uncontrollable," Dr. Olanow said. "The danger is that if you inhibit too much you can induce wild, flinging movements which people have been reported to die from." Once the virus is in the brain, there is no way to get it out or turn it off, he and others pointed out.

But Dr. Kaplitt said the study was being limited to patients who did not like the idea of having a device put in their brain.

Another potential danger is that the virus could spread to other areas of the brain, wreaking destruction, said Dr. Inder Verma, a gene therapy researcher at the Salk Institute, in San Diego, and past president of the American Society of Gene Therapy.

Animal studies indicate that the virus can spread from nerve to nerve, said Dr. Howard Federoff, the director of the Center for Aging and Developmental Biology at the University of Rochester School of Medicine and Dentistry. "That's one thing I felt personally needed to be carefully examined to make sure there weren't going to be any adverse effects," he said.

Even if the virus does not spread in the brain, it could elicit an immune reaction. "You may get a brain inflammation and swelling," Dr. Verma said. "You may lose some neurons."

But Dr. Kaplitt said there was no evidence of any adverse effects in the animal studies except a few transient fevers -- no brain inflammation, and no signs of overproduction of brain chemicals.

Other experts not involved in the trial doubted that the gene therapy would do anything at all.

Dr. Ole Isacson, a professor of neuroscience at Harvard Medical School, said he was not convinced that changing just a single enzyme, with gene therapy, could fundamentally change a nerve cell's nature.

Yet, Dr. Isacson said he was ambivalent about the experiment. "I agree about the many questions," he said. But, he added, "one can say that unless you try bold things in clinical trials it will be very difficult to find what are the most useful paths in the clinical world."

Others, however, said flatly that the experiment was ill advised.

"As a careful and very rigorous person approaching clinical trials, I'd like to see a great deal more data in a nonhuman primate model that the treatment is efficacious and very safe," Dr. Federoff said. He worried that an experiment gone awry could set back gene therapy for years.

So do others.

"I have real theoretical concerns," said Dr. J. William Langston, director of the Parkinson's Institute in Sunnyvale, Calif. "This is really terra incognita, and I'm not sure
we're ready to go there yet, particularly with this strategy."

Mr. Klein did not see it that way. As soon as his doctor told him about the study, he said, he wanted to participate. He found the side effects of the drugs intolerable, his Parkinson's was worsening and a deep brain stimulator did not appeal to him because he did not much like the idea of hardware being left in his brain. He called his doctor every few weeks to check on the project, and did not give up until he was in.

During the procedure yesterday, he was wide awake and in good spirits, joking with doctors and nurses despite having had a metal scaffolding screwed into his head and bolted to the operating table to keep him still and aid in the mapping of his brain. The procedure took about five hours, including an hour and a half to pump the genes into his brain. Soon after it was over, Mr. Klein was settled into a regular hospital room, eating fruit salad, asking for ice cream and getting ready to stroll the corridors.

And hoping for results in the months ahead.

"If it helps me out that's great," Mr. Klein said. "If it helps other people with Parkinson's that's even better."

Correction: August 22, 2003, Friday A front-page article on Tuesday about a gene therapy experiment for Parkinson's disease misstated the given name of a University of Auckland professor who helped develop the experiment. He is Dr. Matthew During, not Michael.

**CAPTIONS:** Photo: Dr. Michael Kaplitt injected particles into the brain of Nathan Klein at New York-Presbyterian Hospital yesterday. The experiment made Mr. Klein the first person to undergo gene therapy for Parkinson's disease. (Photo by Amelia Panico)(pg. A18)